MEDICAL STAFF CONFERENCE

Choriocarcinoma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. BAGSHAW:* The patient is a 23-year-old Caucasian housewife who was admitted to the Cancer Research Institute 23 June 1968 for further evaluation and treatment of known choriocarcinoma.

From the time of her birth through April 1968, she was in good health. She had a normal menarche and subsequent menstrual history, and had two uncomplicated deliveries. On 22 April 1968, she delivered a 12-pound stillborn infant. The postpartum period was complicated by continued uterine bleeding. On 29 May 1968, she was admitted to a local hospital, where she received a blood transfusion because of anemia, and dilatation and curettage were performed. The pathologist's report indicated choriocarcinoma of the uterine tissue. In subsequent studies a Gravindex was positive and no abnormality was seen on an x-ray film of the chest. On 5 June 1968, a total abdominal hysterectomy was performed and the pathologist's report confirmed the diagnosis of choriocarcinoma. The Gravindex at that time was again positive, and another roentgenogram of the chest showed areas of density on both sides. On admission to the Clinical Unit of the Cancer Research Institute (23 June 1968) the past history, review of systems and family history were essentially non-contributory. The patient was well developed and appeared well nourished and in no distress. The only significant finding on physical examination was discharge of a brownish fluid from the vagina. Small nodules were noted on the anterior wall of the vagina on pelvic examination.

The significant laboratory findings at the time of admission were as follows: hematocrit, 26.2 percent; leukocytes 3,900 per cu mm, with a normal differential determination; platelets, 936,000 per cu mm. Urinalysis showed the presence of 40 to 60 white cells per high-power field. All chemical features were within normal limits, except for slight elevation of alkaline phosphatase (4.4 B-L units) and a bromsulphalein retention was 5.9 percent. An x-ray film of the chest showed multiple densities bilaterally. A bone survey was negative. Determinations of 24-hour urinary chorionic gonadotropin were positive at 75,000 international units per 1,000 ml, negative at 90,000 units.

The patient continued to have vaginal bleeding which required transfusion replacement of blood and vaginal packing. Difficulty in voiding necessitated use of a Foley catheter. Because of the previously noted leukopenia, it was decided to start actinomycin D therapy. On 26 June 1 mg was given intravenously and then 0.5 mg a day for the next seven days. The patient also received vincristine, 0.5 mg on 28 June and 0.5 mg on 5 July.

DR. PREGER:* The chest film shows metastatic lesions. If we had obtained tomograms of both lungs, we would have seen additional lesions. An intravenous pyelogram does not show any abnormality of the kidney or evidence of any mass above the bladder. In summary, we have a patient with diffuse pulmonary metastatic lesions.

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*Leslie Preger, M.D., Assistant Professor of Radiology.

DR. SMITH:* The patient is unable to be here for personal presentation this morning. We have asked Dr. Edwin M. Jacobs to open the discussion. As we know, this disorder has been the most promising malignant lesion with regard to therapy. We would like to ask Dr. Jacobs, who has had extensive personal experience, to tell us something about the natural history of choriocarcinoma and something about the result of chemotherapy. More specifically, we would ask: What would you do for this patient, and what would you anticipate?

DR. JACOBS:† The problem presented by this patient is somewhat more complicated than the usual one of choriocarcinoma of the uterus, because she has had a number of complications. She has had vaginal bleeding which has persisted after hysterectomy and, for some unexplained reason, she has had leukopenia although her bone marrow appears to be within normal limits. Most patients with choriocarcinoma of the uterus are treated with an antifolic acid agent, Methotrexate®, in large daily doses. However, we felt that this would be unwise in this patient because of the continued bleeding and the compromised white count. At present we are using actinomycin D in conjunction with vincristine.

As Dr. Smith commented, this is one of the malignant diseases most exciting to treat. This condition allows the first encouraging results we have had in treating patients with widespread metastatic disease with chemotherapy. In fact this is the only cancer we can regularly cure by the use of a drug. The first report of such cures was published by Li in 1956.[8] Apparently this information is still not fully appreciated, so I think we should review briefly our general approach to the diagnosis and treatment of trophoblastic disease at the beginning of this discussion. The details of diagnostic procedures and our approach to therapy are outlined in a recent paper.[7]

First, one should suspect trophoblastic disease after an abnormal pregnancy, abortion, or delivery of a hydatidiform mole, if there is postpartum bleeding or persistence of a positive chorionic gonadotropin titer. One should suspect the disease when there is abnormal bleeding, chest pain, hemoptysis, dyspnea,[2] an unusually large and firm uterus, other masses in the abdomen, or neurological abnormalities (because of the possibility of brain metastasis). Dilatation and curettage should be performed promptly. The patient should also have a complete physical examination and a chest roentgenogram to determine if there is any evidence of metastasis. Of diagnostic value too is a 24-hour urine collection for determination of gonadotropin level. The determination should be performed by an accurate quantitative method in a qualified laboratory. An ordinary pregnancy test will not suffice. If the patient has choriocarcinoma, the chest film and intravenous pyelograms may show some abnormalities. The laboratory studies will show a high chorionic gonadotropin titer because the tumor contains trophoblastic tissue, and the cells are still active endocrinologically and secrete chorionic gonadotropin. They occasionally secrete other hormones, including a TSH-like substance, and in a few patients frank hyperthyroidism may develop as a consequence.[3] Thus, trophoblastic cells have an endocrine marker indicating their presence in the body.

If a diagnosis of choriocarcinoma is established or suspected on the basis of these studies, chemotherapy should be started immediately, for time is of the essence. The disease can progress rapidly. Dr. Hertz (National Cancer Institute), in a study of a large series of cases,[6] found that the patients with the best therapeutic responses were those who were treated within four months after appearance of their first symptoms. The patients who had a poor response or became resistant to chemotherapy were most likely to be those treated later than four months after diagnosis.

Even if the initial dilatation and curettage do not definitely indicate choriocarcinoma, the patient should be observed carefully during the ensuing month. If the findings are negative except for a positive gonadotropin titer, one should draw the conclusion that trophoblastic cells are present, and the patient should be treated, even though this titer might represent a more benign disease than choriocarcinoma. Hysterectomy should not be performed except to prevent bleeding. If the uterus can be spared, the patient's child-bearing potential is not sacrificed. If metastatic disease is going to be cured, the local disease will also be cured. Also, there is no good evidence that hysterectomy will aid in the cure of metastatic disease. According to Hertz, there is some evidence that those patients who have hysterectomy tend to have a poorer prognosis than those who do not.[6]

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We do not know why trophoblastic tissue of the placenta becomes malignant. A hydatidiform mole may develop, or one of the more malignant entities may develop. The etiology is unknown.

The incidence of hydatidiform moles in the United States is one in every 2,000 pregnancies, and about 5 percent of these become choriocarcinoma (that is 1:20,000-40,000 pregnancies). This is a relatively rare disease in the United States. By comparison, in the Philippines[1] the incidences of moles and of choriocarcinoma are considerably higher (moles, 1:200 pregnancies; choriocarcinoma, 1:2,000 pregnancies). This is thought to be due to childbearing at the extremes of the age range and to the high parity of most women in that country. Approximately 50 percent of choriocarcinomas occur after the passage of a hydatidiform mole, approximately 25 percent after an abortion, 22.5 percent after a normal pregnancy, and perhaps 2.5 percent after an ectopic pregnancy.

Trophoblastic disease has been recognized for many centuries. Tumors of the trophoblast were described by Marshand in 1895-1903. A pathologic classification was introduced by James Ewing in 1910. This was a somewhat complicated classification. There is a simplified one now: normal trophoblast, hydatidiform mole, chorioadenoma destruens (that is, malignant mole with local invasion or distant spread), and choriocarcinoma. There is no absolute pathologic distinction between these various types, which form a spectrum, and are now referred to as diseases of the trophoblast.

A considerable body of data obtained in recent decades gives us some interesting facts.[12] It has long been known that trophoblastic tissue does get into the blood vessels of pregnant women, and it has been thought that these emboli might play a role in eclampsia. There have been some early reports of deaths related to emboli. Experimental embolization in animals over many years showed no evidence of eclampsia. During the period 1949-1957 it was recognized that the trophoblastic tissue was a form of homotransplant. It has been referred to as an F_1 hybrid back-cross because half of the chromatin is from the female and half from the male. In other words, the trophoblastic tissue is a product of conception, and is a back-cross to the female. In certain strains of mice, tissue from female transplanted to female, or tissue from male transplanted to male, almost always "takes." But when tissue is transplanted from male to female, there are failures. It has been postulated that the presence of the Y chromosome results in the production of RNA of different base composition.

All of these factors might relate to the interesting fact that trophoblastic malignant lesions can be cured with chemotherapy and other malignant lesions can not.[9] It may be that a genetic difference plays a role. For example, Dr. Page* and coworkers have reported on the sex chromatin content of trophoblastic tumors.[11] They have shown that in hydatidiform moles almost 100 percent are of the XX type, whereas in choriocarcinoma they were mixed. One wonders if the response of patients with choriocarcinoma or their lack of response may in some way be related to whether the choriocarcinoma in a given instance is of the XX or XY type. This has not been fully worked out as yet.

In vitro cultures of trophoblast have been attempted, and human trophoblastic cells have been grown in the anterior chamber of the eye and in the cheek-pouch of cortisone-treated hamsters. All of these studies were attempted to demonstrate the presence of antibodies against trophoblastic tissue. It was thought that unusually good response in a patient might reflect antibody response against this form of transplant, but so far specific antibodies have not been discovered.

Spontaneous remissions have been reported in the range between 5 percent and 20 percent; these have been observed in patients with localized or relatively localized disease. In contrast, I do not know of a case of advanced metastatic choriocarcinoma in which spontaneous remission has occurred.

Early attempts at treatment were made by using antisera to trophoblast in these patients, and in one instance leukocytes from the husband were given to the wife. These results were equivocal at best. Finally in 1956, Dr. Li treated a patient for the first time with large doses of 4-amino-n[10] methyl pteroylglutamic acid (Methotrexate). Some of the background of this form of therapy is of interest. Hertz in 1948 showed that there was decreased development of the genital tracts in folic acid-deficient rats. Nelson and Evans (1951) later demonstrated a high fetal requirement of folate; and Thiersch (1953) found that abortion might result from the use of aminopterin, an anti-folic acid compound. In 1953 at the Memorial Center

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for Cancer and Allied Diseases, New York, Li studied a patient with malignant melanoma who had elevated chorionic gonadotropin titer. The reason for the elevated titer was not explained, but when this patient was treated with Methotrexate, it was noted that the titer dropped. Three years later, when Li (then at the National Cancer Institute) had a patient with widespread chorionic carcinoma, he recalled his earlier chance experience and decided to use Methotrexate in high dosage to treat this patient.

A number of other chemotherapeutic compounds have been used. Karnofsky in 1950 treated a patient with nitrogen mustard (mechlorethamine hydrochloride) and obtained a transient remission of pulmonary metastatic lesions. But it was the introduction of Methotrexate in high daily doses by Li and Hertz[4,8,11] that first led to a significant number of cures. Actinomycin D, an anti-tumor antibiotic, has also been used. Two of the alkaloid extracts of the periwinkle plant, vincristine and vinblastine, have been used. Also 6-diazo-5-oxy-1-norleucine (DON) which is a glutamine antagonist, has been used successfully in treating some patients. In 1964, Dr. Hertz summarized the experience from the National Cancer Institute with various forms of treatment, mainly Methotrexate and actinomycin D, and reported a total response rate of about 64 percent.[5] In a more recent report over 70 percent of women with choriocarcinoma have been found to respond.[6] In our series of cases at the University of California San Francisco Medical Center,[7] we found that before chemotherapy was used no patients survived, even when disease was localized, with the single exception of a patient who had hysterectomy. Since then, with chemotherapy our cure rate has been 90 percent. One patient who entered the hospital in a terminal state with brain metastasis died within three days. In another patient cerebral hemorrhage developed after a complete radiological remission of disease. (See Table 1.)

I will present very briefly several representative cases. The first patient had metastasis to the abdomen, liver, lungs, and brain with many secondary complications. She was treated with 13 courses of Methotrexate over a period of 15 months but is alive and well today, now eight years later. An intravenous pyelogram in April of 1960 revealed hydronephrosis, massive on the right, moderate on the left. A post-therapy intravenous pyelogram showed a normal left kidney and residual hydronephrosis of the right kidney due to fibrosis. Serial x-ray films of the chest showed complete regression of numerous metastatic lesions.

Another patient, who was treated with ten courses of Methotrexate, had a relapse and subsequently was treated with actinomycin D. This patient required hysterectomy because of massive vaginal bleeding during therapy. Intravenous pyelograms during therapy indicated disappearance of abnormalities. The chest film of September 1963 showed massive pulmonary metastatic involvement. These lesions had disappeared by April 1965, and subsequent films have remained clear.

A third patient was treated with massive doses of Methotrexate with no response and was then treated with actinomycin D and chlorambucil, still with no response. She had massive pulmonary infiltrates, dyspnea and bone marrow depression. She was then treated with small doses of vincristine, once weekly. The disease has been in complete remission for the past three years. (See Chart 1 and Figure 1.)

Finally, I will describe one of Dr. Li's cases. The patient had metastatic choriocarcinoma and a high chorionic gonadotropin titer, and was

TABLE 1.—*Toxic Manifestations Associated with Chemotherapeutic Agents Used in Choriocarcinoma of the Uterus*

Agents	*Route of Administration*	*Usual Dose*	*Acute Toxic Signs*	*Major Toxic Manifestations*
4-amino-n[10] methyl pteroylglutamic acid (Methotrexate®)	Intravenous	15 to 20 mg/day × 3 or 5	None	Oral and digestive tract ulcerations; bone marrow depression with leukopenia, thrombocytopenia, bleeding.
Dactinomycin (Actinomycin D)	Intravenous	0.01 mg/kg/day × 4 or 5 every 1-2 weeks or 0.04 mg/kg/ week	Nausea and vomiting	Stomatitis, gastrointestinal disturbances, alopecia, bone marrow depression.
Vinblastine (Velban®)	Intravenous	0.1 to 0.2 mg/kg weekly	Nausea and vomiting	Alopecia, areflexia, bone marrow depression.
Vincristine (Oncovin®)	Intravenous	0.01 to 0.025 mg/kg weekly	None	Areflexia, muscular weakness, peripheral neuritis, paralytic ileus, mild bone marrow depression.

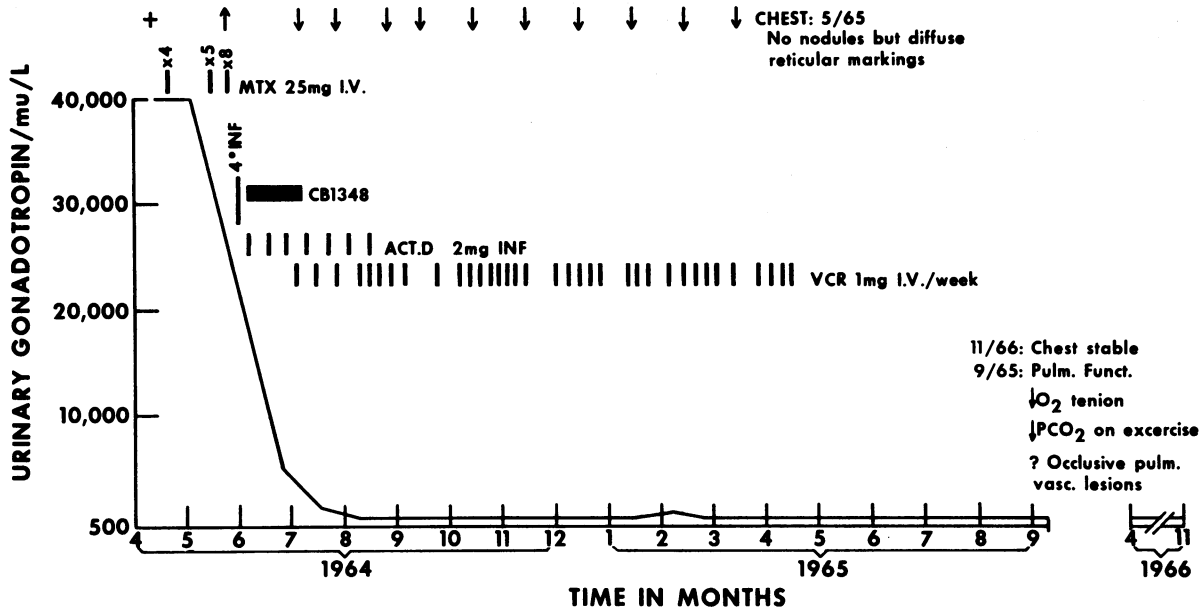

Chart 1.—Response to treatment of a patient with metastatic choriocarcinoma. No response to Methotrexate, actinomycin D, and chlorambucil. Complete remission with vincristine.

treated with Methotrexate. After apparent complete remission of disease and return of gonadotropin titer to zero, therapy was stopped. Subsequently the titer became elevated, and treatment was started again, but this time without alteration of the gonadotropin titer. The patient was found to be pregnant and, fortunately, gave birth to normal twins.

After a patient is apparently cured, contraceptive measures should be used during the following year. Since the gonadotropin titer is a major indicator of recurrence of disease or presence of trophoblastic cells, one may be treating pregnancy rather than recurrence unless alert to this possibility. It is simpler to follow the patient's progress if the possibility of pregnancy is eliminated. After a year of remission of disease, it is safe for her to become pregnant. Pregnancy appears not to increase danger of the occurrence of another choriocarcinoma. I know of no patient who has been cured for a year or more and then had relapse.

DR. SMITH: Thank you very much, Dr. Jacobs. You have brought out some very interesting facts concerning this group of malignant diseases, perhaps one of the most intriguing being that this represents the only malignant homotransplant. I don't think we have another example of a malignant homotransplant in a host, or one which has such an exquisitely sensitive biochemical marker in the form of chorionic gonadotropin to indicate whether malignant cells are present. Finally, there is the sensitivity to chemotherapy. You have answered one of my questions, which was whether choriocarcinoma was rather selectively sensitive.

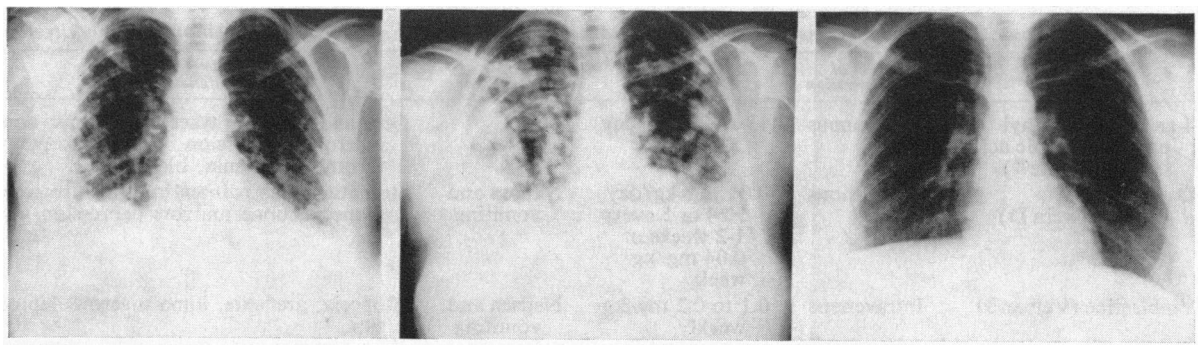

Figure 1.—Chest roentgenograms before therapy (left); showing disease progression after Methotrexate (center), and regression of metastases after vincristine (right).

Apparently, choriocarcinoma responds to a variety of chemotherapeutic agents.

QUESTION FROM THE AUDIENCE: Dr. Jacobs, who do you think should treat choriocarcinoma?

DR. JACOBS: This is a rare disease which physicians rarely see, and it is subject to the complications of aggressive chemotherapy, which were illustrated in our patient today. Because of these factors, I think that these patients are best treated by physicians who have had broad experience with this disease.

QUESTIONS FROM THE AUDIENCE: What is the response of male choriocarcinoma?

DR. JACOBS: The response of male choriocarcinoma is dismal. These tumors do secrete chorionic gonadotropins, and the titer is used as an indicator for therapy. However, these tumors are different genetically since they are autologous. They are very malignant tumors, and their response to chemotherapy is poor.

DR. SMITH: Thank you, Dr. Jacobs.

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SCHOOL PROBLEMS

"[In diagnosing the functional causes of school problems in children,] the most practical thing to do is to go where the trouble is. You cannot sit in your office and find out one tenth of what you can find out in a school in one-fifth the time. I've discovered, particularly in fairly stable schools where the faculty has worked for a good while and where they don't have the 50 or 60 percent turnover characteristic or large urban schools, that you can sit down for about 45 minutes with a collection of teachers, principals, the nurse, perhaps the school physician if you can catch him, and the school social worker and say, 'Tell me why you are concerned, and then let's hear all you know about the family, the brothers and sisters and the parents.' You will find that many of these teachers have taught the parents and also are acquainted with the grandparents. So that quite often in a few minutes you can gather a very rich, detailed, three-generational social, medical, and educational history of a child which would take you weeks and weeks of our usual, laborious clinical interviewing methods to gather."

—STONEWALL B. STICKNEY, M.D., Pittsburgh

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